REMARKS

New claims 45-49 have been added to emphasize that the immunoreactivity is specific for the peptide set forth in claim 32. Since these antibodies are specific for this peptide, they cannot be the same as, or suggested by, antibodies that are immunoreactive with either rat ANP or human ANP. If they were immunoreactive with these peptides, they would, by definition, not be specific for SEQ ID NO: 49.

Applicants appreciate the apparent withdrawal of the previous rejection over Sudoh, *et al.*, in view of Hirth, *et al.* The new rejections are addressed as follows:

Claims 32 and 41-44 were rejected as assertedly anticipated under 35 U.S.C. § 102(e) by Hirth, *et al.* Alternatively, the rejection was for obviousness. The Office postulates that because of certain similarities in portions of their sequences, antibodies prepared by Hirth that are immunoreactive with human ANP would also be useful to detection human BNP.

The Office quotes *In re Spada* for the proposition that when the PTO shows a sound basis for believing that the products of the applicant and prior art are the same, the applicant has the burden of showing that they are not.

Applicants do not concede that a *prima facie* case has been made that the antibodies of Hirth and those claimed are the same. As to new claims 45-49, clearly they are not. However, even if a *prima facie* case had been made, applicants have already demonstrated that they are not the same. Respectfully, applicants refer to their previous response.

The Sudoh article, cited by the Office, demonstrates clearly that antibodies immunoreactive with either rat or human ANP do not immunoreact with porcine BNP. This is evident from several perspectives. First, an examination of figure 1a shows that it is peak B (the black bars) that shows relaxant activity on chick rectum as would be characteristic of BNP. Fraction B was further purified as indicated in figures 1b-1d to isolate the peptide having the

amino acid sequence shown in figure 2 for porcine BNP. There is no overlap of fraction B, which thus contains porcine BNP, with fraction C which is stated clearly in the legend as containing the ANP-like immunoreactivity. This demonstrates that antibodies raised against rat ANP do not crossreact with porcine BNP. They would not be expected to crossreact with human BNP either.

The sequences of rat ANP compared to porcine BNP and human BNP are shown below:

```
                    *  *        **
porcine BNP         CFG RRL DRI GSL SGLGC
rat ANP             CFG GRI DRI GAQ SGLGC
human BNP           CFG RKM DRI SSS SGLGC
                        ***     ***
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As indicated by the asterisks above porcine BNP, this peptide differs in four amino acids from rat ANP, but antibodies prepared against rat ANP failed to detect porcine BNP in the pig brain. A comparison with human ANP is shown by the asterisks below the sequence of human BNP. This sequence differs in six places. Thus, since rat ANP antibodies do not crossreact with porcine BNP with only four differences, it could hardly be expected that these antibodies would crossreact with human BNP with six differences.

Sudoh explicitly states that antibodies raised against human ANP also fail to react with porcine BNP. On page 80, left-hand column,

> The 17 amino-acid sequence (α-ANP[7-23]) flanked by two Cys residues, thought to be essential for ANP activity, is highly conserved in the molecule of pBNP, although four residues in this region are replaced. *This may explain the fact that pBNP does not crossreact with anti-α-hANP-antibody*[13]*, which is only 20% crossreactive even with rat α-ANP(α-rANP)*, which has only a single replacement (Met-to-Ile) at position 12 (see Fig. 1 legend). (Emphasis added.)

The lack of crossreactivity is referenced to document 13 – Miyata, A., *et al., Biochem. Biophys. Res. Commun.* (1987) 142:461-467, - which describes the preparation of antibodies to human

ANP. Thus, Sudoh clearly states that antibodies raised against human ANP, i.e. those of Hirth, do not crossreact with porcine BNP.

Since this is the case, would it then be expected that crossreactivity would occur with respect to human BNP? The amino acid sequences of porcine BNP, human ANP, and human BNP in the critical 17 amino acid portion bracketed by cysteines are shown.

```
                      * *     **
porcine BNP     CFG RRL DRI GSL SGLGC
human ANP       CFG GRM DRI GAQ SGLGC
human BNP       CFG RKM DRI SSS SGLGC
                    **      ***
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As shown by the asterisks above the porcine BNP sequence, it differs from that of human ANP in four positions. As shown by the asterisks below the sequence of human BNP, the amino acid sequence of human BNP differs from human ANP in five positions, three of which are the same as those wherein porcine ANP differs. Thus, the amino acid sequence of human BNP is even more different from human ANP than is that of porcine BNP. Since porcine BNP and antibodies raised against human ANP do not crossreact, it would clearly not be expected that antibodies raised against human ANP would crossreact with human BNP.

Respectfully, applicants believe they <u>have</u> submitted the evidence required to show that the antibodies claimed are not the same as those in the art.

With respect to the rejection for obviousness, made in the alternative, applicants see no rationale in support of this rejection. It clearly cannot be obvious over the prior art since the prior art fails even to disclose the amino acid sequence of human BNP.

Claim 32 was rejected as assertedly anticipated or alternatively as obvious over Sudoh, *et al.*

Respectfully, it appears that Sudoh has not been correctly characterized. As outlined in the previous response, the fractions with "ANP-like" immunoreactivity, if tested further for

relaxant activity apparently showed none. This is apparent, as stated above, from figure 1a where fraction B which shows relaxant activity is clearly not the same as fraction C which has immunoreactive activity. Thus, it is apparent that the antibodies (to rat ANP) used by Sudoh were not, as asserted by the Office, "used to identify porcine brain natriuretic peptide." On the contrary, these antibodies failed to react with porcine BNP which was in a completely different fraction. Thus, Sudoh itself shows the asserted obligation set forth in *In re Spada* has been met.

Again, with respect to the rejection in the alternative for obviousness, no rationale in support of this rejection is provided. The Office is again reminded that the amino acid sequence for human BNP was not known at the time the original application was filed; therefore the preparation of antibodies to this amino acid sequence could not have been suggested by the art.

CONCLUSION

It has been demonstrated that neither antibodies raised against human ANP nor those raised against rat ANP are immunoreactive with porcine BNP. Since porcine BNP differs from human ANP even less than does human BNP, it can be concluded that the antibodies disclosed by Sudoh and those disclosed by Hirth do not anticipate or render obvious the antibodies claimed. Accordingly, applicants respectfully request that claims 32 and 41-49 be passed to issue forthwith.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 219002025213.

Respectfully submitted,

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